REMARKS

Claims 3-6, 11, and 13-16 are pending in the present application and are under examination. Applicant reserves the right to pursue any canceled subject matter in a future application.

1. Applicants acknowledge that prosecution has been re-opened in view of the Appeal Brief filed April 11, 2003; and herewith file a reply under 37 CFR § 1.111. Applicants note that the Examiner has not addressed any of Applicants' arguments set forth in the Appeal Brief with respect to the rejections of record.

Accordingly, Applicants herewith provide a summary of the invention for clarification purposes.

The specification states, at page 6, lines 20-31 that: "The present invention provides, in one aspect, pharmaceutical preparations for use in tolerizing individuals to autoantigens. The preparations include a pharmaceutically acceptable carrier and an isolated human polypeptide which includes an amino acid sequence corresponding to a sequence motif for an HLA-DR protein which is associated with a human autoimmune disease. These polypeptides are capable of binding to the HLA-DR protein to form a complex which activates autoreactive T cells in subjects having the autoimmune disease. The peptides are not derived from human collagen or human myelin basic protein."

The specification states, at page 7, lines 1-10: "In particular embodiments, such pharmaceutical preparations are provided in which the HLA-DR protein is HLA-DR4 protein and the autoimmune disease is pemphigus vulgaris. In addition, a particular sequence motif is provided for pemphigus vulgaris and pharmaceuticals having peptides with this motif are

provided. Specific embodiments of the pharmaceuticals include each of the polypeptides described above with respect to pemphigus vulgaris. Thus, methods of tolerizing an individual to a pemphigus vulgaris autoantigen are also provided."

The specification states, at page 7, lines 11-21: "In another set of embodiments, the invention provides for pharmaceutical preparations for use in tolerizing individuals to antigens of human pathogens which are implicated in human autoimmune disease. The preparations include a pharmaceutically acceptable carrier and an isolated human pathogen polypeptide which includes an amino acid sequence corresponding to a sequence motif for an HLA-DR protein which is associated with a human autoimmune disease. These polypeptides are capable of binding to the HLA-DR protein to form a complex which activates autoreactive T cells in subjects having the autoimmune disease."

The specification states, at page 8, lines 1-14: "In another aspect of the invention, pharmaceuticals are provided for vaccination against a human pathogen implicated in the aetiology of autoimmune disease. These pharmaceutical preparations include a pharmaceutically acceptable carrier and an immunogenic preparation effective to immunize against a human pathogen. The human pathogen is one which in its native form includes a polypeptide having an amino acid sequence corresponding to a sequence motif for an HLA-DR protein which is associated with the autoimmune disease. These polypeptides are capable of binding to the HLA-DR protein to form a complex which activates T cells which become autoreactive and initiate the autoimmune disease. The preparations of the present invention specifically do not include such polypeptides but, rather, include other antigens from the pathogen."

The specification states, at page 8, lines 14-24: "In particular embodiments, such pharmaceutical preparations are provided in which the HLA-DR protein is HLA-DR4 protein and the autoimmune disease is pemphigus vulgaris. In addition, a particular sequence motif is provided for pemphigus vulgaris and pharmaceuticals which lack peptides having this motif are provided. Specific embodiments of the pharmaceuticals include preparations lacking each of the polypeptides described above with respect to pemphigus vulgaris."

Autoimmune disease is generally defined as the pathological consequences, including tissue injury, produced by autoantibodies or autoreactive T cells interacting with self epitopes. An "epitope" is defined as "an antigenic determinant ... the simplest form or smallest structural area on a complex antigen molecule that can combine with an antibody or T lymphocyte receptor." (The Illustrated Dictionary of Immunology, CRC Press (1995)) Self epitopes are derived from an individual's own proteins. The inappropriate response of the immune system against self epitopes in autoimmune disease can cause serious damage to cells and organs, sometimes with fatal consequences.

The distinction between an antigen and an epitope is critical to the understanding of the present invention. The terms "autoantigen," and "self antigen," as understood in the art and used in the instant specification, refer to a full-length protein or a polypeptide that includes a self epitope which, as stated above, is the simplest form or smallest structural area on a complex antigen molecule that can combine with an antibody or T lymphocyte receptor.

T cell recognition of antigens, including self antigens, involves a tri-molecular complex of (1) a T cell receptor, (2) an MHC molecule, such as HLA-DR, and (3) a short peptide comprising an epitope. (See for example, page 6, lines 27-30, original claims 3 and 13, and

pending claims 3 and 13 which require the that the polypeptides of the invention be "capable of binding to HLA-DR protein to form a complex which activates autoreactive T cells in subject having the autoimmune disease.") When the MHC molecule is a Class II molecule, such as HLA-DR, the peptides derived from antigen are heterogeneous in size. (See page 5, lines 8-10.) Peptides that bind HLA-DR molecules have been reported as ranging in size from 12-25 amino acid long. (See Chicz et al., "Predominantly naturally processed peptides bound to HLA-DR1 are derived from MHC-related molecules and are heterogeneous in size," Nature, 358:764-768 (1992); cited on page 5, at line 10 of the original specification.)

Particular MHC class II molecules (e.g., HLA-DR) have been closely associated with autoimmune disease. For example, HLA-DR4 has been associated with the autoimmune condition pemphigus vulgaris (PV). PV is an autoimmune disease of the skin which is manifested by blistering lesions of the skin and mucous membranes. (See page 2, lines 13-17.)

The present specification teaches methods of identifying peptides that form part of the tri-molecular complex with autoreactive T cells and HLA-DR molecules. Such peptides are useful to treat autoimmune diseases, for example, by inducing high dose tolerance to thereby render autoantigenic T cells unresponsive to self epitope bound to an HLA-DR molecule. (See page 30, lines 14-31 and page 52, lines 11-15.)

A large body of clinical and epidemiological evidence suggests that bacterial or viral infection may trigger the induction of autoimmunity. (See page 3, lines 13-17.) One theory suggests that peptides of a pathogen that closely resembling self peptides "mimic" self epitopes to activate autoreactive T cells and induce autoimmunity. Accordingly, the present invention also provides for methods of vaccinating an individual against an autoimmune condition by

vaccinating the individual against the pathogen with a preparation that specifically excludes autoreactive peptides from the pathogen, that is, peptides that form part of the complex with autoreactive T cells and HLA-DR molecules. (See page 32, lines 9-29.)

35 USC § 112, first paragraph, scope of enablement

2. Claims 3-6, 11, and 13-16 are rejected under 35 USC 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way to fully enable one skilled in the art to make and/or use the invention.

The Examiner has set forth that claims 3-6 and 11, which directly or indirectly recite a "human polypeptide consisting essentially of an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein" are unpatentable under 35 U.S.C. § 112, 1st paragraph as being based on a non-enabling disclosure.

The Examiner has set forth that claim 6, which recites "an amino acid sequence consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ ID NO.: 6, and SEQ ID NO.: 7" is unpatentable under 35 U.S.C. § 112, 1st paragraph as being based on a non-enabling disclosure.

The Examiner has set forth that claims 13-16, which directly or indirectly recite a "human pathogen that in its native form includes a polypeptide having an amino acid sequence corresponding to the core MHC residues of a sequence motif for an HLA-DR protein" is unpatentable under 35 U.S.C. § 112, 1st paragraph as being based on a non-enabling disclosure.

The Examiner has set forth that claim 16, which recites "an amino acid sequence consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ ID NO.: 6, and SEQ ID NO.: 7" is unpatentable under 35 U.S.C. § 112, 1st paragraph as being based on a non-enabling disclosure.

The Office action states that "the specification, while being enabling for a pharmaceutical preparation comprising a human polypeptide *consisting* of one of SEQ IDS NOS: 1-7, does not reasonably comprise a human polypeptide *consisting essentially* of an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein, nor *consisting essentially* of one of SEQ ID NOS: 1-7." (Emphasis added.)

Applicants' Rebuttal of the Rejection of Claims 3-6 and 11 under 35 U.S.C. § 112, First Paragraph

According to MPEP § 2111.03: "the transitional phrase 'consisting essentially of' limits the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention." MPEP § 2111.03, quoting In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (C.C.P.A. 1976) (emphasis in original). "A 'consisting essentially of' claim occupies a middle ground between closed claims that are written in a 'consisting of' format and fully open claims that are drafted in a 'comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). The phrase "consisting essentially of "exclude[s] additional unspecified ingredients which would affect the basic and novel characteristics of the product defined in the balance of the claim." In re Garnero, 412 F.2d 276, 279, 162 USPQ 221, 223 (C.C.P.A. 1969).

As explained below, Applicants have clearly identified the "basic and novel characteristics" of the present invention and therefore the "consisting essentially of" phrase should be construed as open to those materials that do not materially affect the basic and novel characteristics and closed to those materials that do materially affect the basic and novel characteristics of the claimed invention.

In brief, the present application teaches methods of "defining those amino acids of the self or non-self antigen that are needed for MHC binding and TCR [T cell receptor] contact" so that "self epitopes involved in autoimmune disease may be identified." (See page 5, lines 24-31.) It is these self epitopes (and non-self epitopes that mimic self epitopes) that are, the active agents of the pharmaceutical preparations for tolerization recited in claims 3-6 and 11. Accordingly, the basic and novel characteristics of the claimed polypeptides include the ability (1) bind to HLA-DR protein and (2) activate autoreactive T cells from a subject having an autoimmune disease.

Applicants submit that independent claim 3 (as well as claims 4-6 and 11 that depend from claim 3) which claims polypeptides that "consist essentially of an amino acid sequence corresponding to the core MHC binding residues of the sequence motif for an HLA-DR molecule ... [which] binds to said HLA-DR protein [and] activates autoreactive T cells from a subject having said autoimmune disease" embraces only polypeptides that bind to HLA-DR and activate autoreactive T cells, and specifically excludes peptides that are incapable of binding to HLA-DR and/or activating autoreactive T cells.

Furthermore, the specification expressly states that "peptides including at least the MHC binding and TCR contact residues are contemplated as equivalents." (See page 28, lines 27-30.)

Thus, the present specification clearly indicates that the basic and novel characteristics of the claimed polypeptides are the ability to (1) bind to HLA-DR protein and (2) activate autoreactive T cells from a subject having an autoimmune disease. Furthermore, the claims explicitly require that the preparations of the invention comprise polypeptide that "binds to [said] HAL-DR protein" and "activates autoreactive T cells."

For the foregoing reasons, Applicants submit that the instant specification fully enables pending claims 3-6 and 11 when the term "consisting essentially of" is interpreted properly as partially open and partially closed. Under this construction of the "consisting essentially of" phrase, claims 3-6 and 11 include polypeptides with an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for HLADR protein and other components (e.g., additional amino acids) that do not materially affect the ability of the polypeptides to bind to HLA-DR molecules and activate autoreactive T cells from a subject having an autoimmune disease.

Full-length proteins or long polypeptides do not fall within the scope of claims 3-6 and 11 because, as was notoriously well known in the art at the time the application was filed, MHC molecules do not bind full-length proteins or long polypeptides from an antigen. MHC molecules bind short peptides that are small fragments of an antigen. The distinction between an antigen and an epitope is critical to the understanding of the present invention. The terms "autoantigen," and "self antigen," as understood in the art and used in the instant specification, refers to full-length protein or polypeptide that includes a self epitope. As stated above, an "epitope" is an antigenic determinant ... the simplest form or smallest structural area on a complex antigen molecule that can combine with an antibody or T lymphocyte receptor.

The present application is directed to identification of self epitopes and preparations that utilize such self epitopes. The present specification explains that although the target antigens implicated in the immunopathogenesis of disease have been identified, specific self epitopes have not been identified. See, for example, page 23, lines 15-20, which reads: "An ever increasing number of autoimmune diseases are now being associated with particular alleles of the MHC class II HLA-DR locus. For most of these autoimmune diseases, the self epitope remains unknown. For some, however, the self protein involved in autoimmune response is known or suspected. In one aspect of the present invention, a method is provided for identifying the self epitopes involved in autoimmune diseases associated with HLA-DR alleles." (Emphasis added.) The pharmaceutical preparations of claims 3-6 and the method of claim 11 utilize these self epitopes to tolerize (i.e., render autoreactive T cells unresponsive to the self epitope, see page 52, lines 12-17) an individual to an autoantigen through MHC class II presentation.

The specification reiterates the distinction between an autoantigen and self epitope in the description of the autoimmune disease pemphigus vulgaris at page 37, lines 16-23 "Although the autoantigen for pemphigus vulgaris is known, the precise epitopes within the autoantigen have previously remained unknown. Using the methods of the present invention, it has been possible to identify a small set of peptides that may serve as the autoantigenic determinants. The target antigen of pemphigus vulgaris is an epithelial adhesion molecule of the cadherin family, desmoglein 3 (Amagai et al., 1991)." As stated in the Abstract, "The peptides relating to pemphigus vulgaris are self epitopes," thus, the polypeptides recited in claims 3-6 and 11 are essentially self epitopes that form part of the HLA-DR/T cell receptor/peptide complex that causes autoimmune disease and they are necessarily relatively small peptides.

Furthermore, the working examples of the polypeptides of the invention that are disclosed in the instant specification (SEQ ID NO. 1-7) are peptides that are 15 amino acids long, "partly as a result of the computer database search program used (Genetics Computer Group program "Find patterns") but also *corresponding to the size of the cleft in MHC class II molecules*." (See page 37, lines 10-14; emphasis added.) Thus, the instant specification teaches that polypeptides capable of binding to HLA-DR proteins may be approximately 15 amino acids long. However, the instant specification also teaches that shorter or longer peptides "may have utility" and thus, "fall within the spirit and the scope of the claims" (See page 28, lines 16-30.) Thus, pending claim 3 which recites a pharmaceutical preparation for tolerization ... consisting essentially of an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA DR protein, ... [which] binds to said HLA-DR protein [and] activates autoreactive T cells" embraces polypeptides that consist of self epitopes (which may be heterogeneous in size) and excludes full length proteins and large protein fragments that are too large to form the HLA-DR/T cell receptor/peptide complex.

The Office action suggests that "there is no guidance in the specification as to what alterations result in a functional polypeptide, i.e., one that binds HLA-DR." (Emphasis added.) Applicants submit that the present specification provides detailed analysis of the binding pockets of HLA-DR molecules which properly teaches the skilled artisan how to predict which peptides are capable of binding to HLA-DR molecules. For example, the claims 5 and 15 provide a motif to identify peptides that are capable binding to HLA-DR molecules and activating T cells associated with the autoimmune disease pemphigus vulgaris.

The Office action also suggests that undue experimentation would be required to determine what substitutions would be acceptable to retain functional activity. Applicants note

that "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Moreover, Applicants submit that neither "extensive experimentation" nor "undue experimentation" is required to practice the claimed invention.

The identification of amino acid sequences that have functional activity including the ability to bind to HLA-DR proteins and to activate autoreactive T cells may be readily determined by various assays that were well known to the skilled artisan at the time the present application was filed. For example, functional activity may determined using the T cell proliferation assay described in Example 1 of the specification at page 44, lines 11-22.

According to MPEP § 2164.01: "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff d. sub nom. Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)." MPEP § 2164.01. The specification teaches, at page 25, lines 3-13, that the peptides of the invention may be screened for activity using experimentation that is typical in the art, for example, by "*in vitro* tests for the ability to induce the proliferation of autoreactive T cells or to induce the secretion of lymphokines (cytokines) from these T cells or to induce other effector functions such as cytotoxicity." Accordingly, Applicants submit that undue experimentation is not required to practice the claimed invention.

The Office action cites the Ngo reference ("The Protein Folding Problem and Tertiary Structure Prediction," Merz & LeGrans, Birkhauser, Boston, pages 491-495, 1994) to support the assertion that the relationship between the sequence of a polypeptide and the tertiary structure is

not predictable. As is well known in the art, proteins are cleaved into fragments of approximately 12-25 amino acids and bound in the binding cleft of the HLA-DR molecule in an unfolded or essentially linear conformation. See page 116 of Cellular and Molecular Immunology, attached at Appendix D, which states "T cells recognize only linear determinants of peptides defined predominantly by primary amino acid sequences that assume extended confirmations within the peptide-binding clefts of MHC molecules." Thus, the tertiary structure of the peptide does not materially impact the ability of a self epitope polypeptide to bind to HLA-DR molecules and activate autoreactive T cells. Accordingly, Applicants submit that the difficulty in predicting the folding pattern or tertiary structure of full-length proteins discussed in Ngo is irrelevant to the ability of the peptides of the invention to bind to HLA-DR molecules and/or activate autoreactive T cells.

Claims 3-6 and 11 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement. In particular, the Office action suggested that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As discussed above, Applicants have respectfully requested that the rejections of claims 3-6 and 11 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Applicants' Further Rebuttal of the Rejection of Claims 6 and 11 under 35 U.S.C. §112, First Paragraph

Claim 6 depends from claim 4, which depends in turn from claim 3. "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers." 35 U.S.C. § 112, fourth paragraph (2003). Claim 4 requires an isolated human

polypeptide that binds to HLA-DR4 protein and, bound to HLA-DR4 protein, activates autoreactive T cells from a subject having pemphigus vulgaris. Claim 6 requires that the polypeptide consist essentially of an amino acid sequence consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NOs.: 1-7.

The transition "consisting essentially of" excludes from the amino acid sequence of claim 6 additional moieties materially affecting the basic and novel characteristics of the product. As set forth within the claims themselves and in the specification, the basic and novel characteristics of the polypeptide of claim 6 include that the polypeptide binds to HLA-DR4 protein and that the polypeptide bound to HLA-DR4 protein activates autoreactive T cells from a subject having pemphigus vulgaris. Thus, the amino acid sequence is closed to the presence of additional moieties materially affecting the ability of the polypeptide to bind to HLA-DR4 protein and to activate autoreactive T cells from a subject having pemphigus vulgaris.

Claim 11 depends in the alternative from claims 4-6 and incorporates by reference all of the limitations of the particular claim in relation to which it is being considered. See 35 U.S.C. § 112, fifth paragraph (2003).

The outstanding rejection of claims 6 and 11 acknowledges that the specification enables pharmaceutical preparations "comprising a human polypeptide consisting of one of SEQ ID NOS: 1-7." Thus, the only question is whether the specification also enables pharmaceutical preparations comprising human polypeptides with one or more additional moieties that do not materially affect the ability of the polypeptide to bind to HLA-DR4 protein and to activate autoreactive T cells from a subject having pemphigus vulgaris.

Many of the arguments made in the Office action to support the rejections of claims 3-6, 11 and 13-16 are irrelevant to claim 6. To support the rejection of claims 3-6, 11 and 13-16 under 35 U.S.C. § 112, the Office action asserts that "the amino acids at a maximum of three of the motif positions may not be motif amino acids and may actually be deleterious to binding" and that "extended experimentation ... would be required to determine which substitutions would be acceptable." Neither of these assertions is relevant to claim 6. The polypeptide of claim 6 consists essentially of an amino acid sequence consisting essentially of one of SEQ ID NOs: 1-7. No substitutions within any of the seven SEQ ID NOs are permitted.

The Office action also asserts that the presence of amino acid residues outside the "core" may be deleterious to binding. It is, however, uncontested that peptides 12-25 amino acids in length can bind productively to HLA-DR4. See, e.g., page 28, lines 16-30 of the specification (teaching that shorter or longer peptides "may have utility" and "fall within the spirit and the scope of the claims").

Furthermore, Applicants submit that any experimentation to confirm the ability of a human polypeptide consisting essentially of an amino acid sequence consisting essentially of an amino acid sequence selected from the group consisting essentially of SEQ ID NOs: 1-7 would be routine and not undue. As noted in the specification, for example, functional activity may be determined using a T cell proliferation assay. See page 44, lines 11-22 of the specification. The specification teaches, at page 25, lines 3-13, that the peptides of the invention may be screened for activity using experimentation that is typical in the art, for example, by "*in vitro* tests for the ability to induce the proliferation of autoreactive T cells or to induce the secretion of lymphokines (cytokines) from these T cells or to induce other effector functions such as cytotoxicity." In view of the availability of routine methods to screen the peptides for activity,

the relatively narrow scope of the claims and the express teachings in the specification regarding how to make and use the invention with the high level of skill in the art, Applicants respectfully request that the rejections of claims 6 and 11 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Claims 13-16 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement. In particular, the Office action suggested that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

Applicants note that the Office action also rejected claims 3-6 and 11 under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement. The Office action alleges that claim 13 is not enabled for preparations for immunizing an individual against a "human pathogen that in its native form includes a polypeptide having an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein."

Applicants' Rebuttal to the Rejection of Claims 13-16 under 35 U.S.C. § 112, First Paragraph

The Office action alleges that claim 13 is not enabled for preparations for immunizing an individual against a "human pathogen that in its native form includes a polypeptide having an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein."

"Transitional phrases such as "composed of," "having," or "being" must be interpreted in light of the specification to determine whether open or closed claim language is intended. See,

e.g., Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1573, 43 USPQ2d 1398, 1410 (Fed. Cir. 1997), cert. denied, 118 S. Ct. 1548 (1998) (construing "having," in the context of a cDNA having a sequence coding for human PI, to permit inclusion of other moieties). MPEP § 2111.03.

Applicants note that the objected to phrase recited in claim 13 sets forth the target of the immunization, a pathogen that in its native form includes polypeptides having amino acid sequence corresponding to the core MHC binding residues of a sequence motif; however, the final limitation of the claim requires that the pharmaceutical preparation be free of autoantigens (i.e., peptides with amino acid sequence corresponding to the polypeptide that binds to HLA-DR protein and activates autoreactive T cells from a subject having the autoimmune disease). Thus, the epitopes described in the specification and recited in clams 3-6 and 11 are removed from the preparations of claims 13-16 to vaccinate an individual against a pathogen associated with autoimmune disease without exposing the individual at risk to the autoimmune disease to autoantigens that are native to that pathogen.

The specification teaches that preparation for vaccinating a person at risk of an autoimmune disease of the invention may be used to induce immunity against a pathogen associated with autoimmunity without exposing the individual to the autoantigens associated with the pathogen. Thus, the phrase "having" as used in claim 13 is an open transitional phrase, which includes polypeptides native to the pathogen. However, the "free of the amino acid sequence" corresponding to the core MHC binding residues limitation specifically excludes epitopes that bind to HLA-DR and activate autoreactive T cells.

Applicants submit, for the reasons stated above, that the instant specification properly teaches the skilled artisan how to identify peptides that bind to HLA-DR molecules associated with autoimmune disease and activate autoreactive T cells in a person having such an autoimmune disease. The instant specification further teaches the skilled artisan that an individual at risk of an autoimmune disease associated with a human pathogen can be immunized against the pathogen with a preparation that can include polypeptides of the pathogen but that certainly excludes (i.e., is free of) epitopes that activate autoreactive T cells in a person inflicted with the autoimmune disease.

Claims 13-16 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement. In particular, the Office action suggested that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' Further Rebuttal to the Rejection of Claim 16 under 35 U.S.C. § 112, First Paragraph

Claim 16 depends from claim 14, which in turn depends from claim 13. Thus, claim 16 relates to a pharmaceutical preparation comprising a pharmaceutically acceptable carrier and an amount of an immunogenic preparation effective to immunize against a human pathogen that in its native form includes a polypeptide that binds to HLA-DR4 protein and, bound to the HLA-DR4 protein, activates autoreactive T cells from a subject having pemphigus vulgaris. The immunogenic preparation is free of a polypeptide corresponding to a sequence consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-7.

Applicants submit that it is straightforward, given a known amino acid sequence such as that of elected SEQ ID NO: 3, to omit that sequence from a protein preparation using biochemical or recombinant DNA technologies. If the sequence is absent, the immunogenic preparation will be free of a polypeptide corresponding to a sequence consisting essentially of SEQ ID NO: 3. Accordingly, Applicants submit that preparation of an appropriate pharmaceutical preparation is well within the high level of skill in the art. The instant specification further teaches the skilled artisan that an individual at risk of an autoimmune disease associated with a human pathogen can be immunized against the pathogen with a preparation that can include polypeptides of the pathogen but that certainly excludes (i.e., is free of) epitopes that activate autoreactive T cells in a person inflicted with the autoimmune disease.

In view of the relatively narrow scope of the claims and the express teachings in the application coupled with the high level of skill in the art, Applicants respectfully request that the rejections of claims 3-6, 11, and 13-16 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

35 USC § 112, first paragraph, written description

3. Claims 3-6, 11, and 13-16 are rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner states at page 3 of the Office action that the "specification does not ... provide adequate written description of [a] 'human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an

HLA-DR protein', nor consisting essentially of one of SEQ ID NOS: 1-7, nor of a polypeptide *having* an amino acid sequence *corresponding* to the core MHC binding residues of a sequence motif for an HLA-DR protein, nor does it provide adequate written description of what those MHC core binding residues are ... wherein ... said polypeptide binds to said HLA-DR protein, ... wherein the non-MHC binding residues activates autoreactive T cells from a subject having an autoimmune disease and causes tolerization, nor wherein the HLA-DR protein is associated with a human autoimmune disease. The specification does not disclose what amino acid residues are associated with a *human* polypeptide".

Applicants' rebuttal with respect to each of point of rejection has been discussed *supra*. Applicant can show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). MPEP 2163.02. Further, Applicant is not required to define every species within a genus in order to meet the written description guidelines.

Succinctly, Applicants have provided a detailed description of 16 specific peptides of human polypeptide sequences consisting essentially of SEQ ID NOS: 1-16 which bind to HLA-DR2 or HLA-DR4 and wherein the non-MHC binding residues activate autoreactive T cells from a subject having an autoimmune disease such as , Pemphigus vulgaris (i.e., HLA-DR4) and MS (i.e., HLA-DR2). The specification also sets forth several motifs wherein both the MHC binding residues and T cell receptor binding residues are set forth. Thus, the specification sets forth multiple specific examples of human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR

protein consisting essentially of SEQ ID NOS: 1-16 which are polypeptides *having* an amino acid sequence *corresponding* to the core MHC binding residues of a sequence motif for an HLA-DR protein wherein the MHC core binding residues are defined, which bind to an HLA-DR protein, wherein the non-MHC binding residues activates autoreactive T cells from a subject having an autoimmune disease and cause tolerization, wherein the HLA-DR protein is associated with a human autoimmune disease, and what amino acid residues are associated with a *human* polypeptide

Consequently, not only have Applicants provided 16 species that fit these descriptions, Applicants have also set forth to one skilled in the art how to identify other peptides having these same functional characteristics using the motifs described. Applicants assert that the application as filed provides sufficient support for the claims as currently amended according to MPEP 2163 and the Written Description Guidelines.

Accordingly, Applicants submit that the application as filed provides sufficient written description of the claims as currently recited and respectfully request reconsideration and withdrawal of the rejection.

35 USC § 112, second paragraph

4. Claims 13-16 are rejected under 35 USC 112, second paragraph as allegedly being indefinite.

(a) The Examiner states at page 8 of the Office action that claim 13 is indefinite in the recitation of "wherein said preparation is free of a polypeptide corresponding to said sequence".

Applicants submit that claim 13 clearly claims a pharmaceutical for vaccinating an individual at risk of an autoimmune disease by vaccinating against a human pathogen with a preparations which specifically excludes (is free of) autoantigenic peptides, that is, pathogenic polypeptides corresponding to a sequence motif for HLA-DR protein associated with an autoimmune disease. The text of claim 13 reads as follows:

> A pharmaceutical preparation for vaccinating an individual at risk of an autoimmune disease comprising a pharmaceutically acceptable carrier and
>
> an amount of an immunogenic preparation effective to *immunize against a human pathogen that in its native form includes a polypeptide having an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein*;
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> wherein said sequence motif for said HLA-DR protein is based upon the structure of the HLA-DR binding site
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> wherein said HLA-DR protein is associated with said autoimmune disease;
>
> wherein said polypeptide binds to said HLA-DR protein;
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> wherein said polypeptide bound to said HLA-DR protein activates autoreactive T cells from a subject having said autoimmune disease; and
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> wherein said preparation is *free of a polypeptide corresponding to said sequence.* (Emphasis added.)

The Office action suggests that the phrase "free of a polypeptide corresponding to said sequence" is indefinite. Applicants submit that this phrase is amenable to a single interpretation, specifically, the preparation is free of autoantigenic peptides, that is, peptides that bind to HLA-DR and activate autoreactive T cells are not present in the pharmaceutical preparation.

(b) The Examiner states at page 8 of the Office action that claim 13 is indefinite in the recitation of "includes a polypeptide" because it is not clear whether said polypeptide is a portion

of a protein from a pathogenic organism. This phrase, taken in the context of the limitation "immunize against a human pathogen that in its native form includes a polypeptide having an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein" clearly indicates that the polypeptide recited in claim 13 is a portion of a protein from the pathogenic organism.

Applicants submit that claim 13 satisfies the requirements of 35 U.S.C. § 112, second paragraph, respectfully request that the rejection of claim 13 and claims 14-16 (which depend from claim 13) under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Obviousness-type double patenting

5. Claims 3-6 and 13-16 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 3 of U.S. Patent 5,874,531.

The Office action states that "although the conflicting claims are not identical, they are patentably indistinct from each other because the composition comprising the peptides of claim 3 of the '531 patent are encompassed by the instant claims. Applicants note that the instant application is a division of the application that issued as the '531 patent and, as such, 35 U.S.C. § 121 prohibits the use of the '531 patent as a reference against the instant application. Thus, Applicants respectfully request that the double patenting rejection over claim 3 of the '531 patent be reconsidered and withdrawn.

35 USC § 102(b)

6. Claims 3-5 and 13-15 stand rejected under 35 USC 102(b) for allegedly being anticipated by Amagai et al. (Cell 1991, 67: 869-877) for the reasons of record in Paper No. 12, mailed June 16, 1999.

As stated above, with regard the § 112, first paragraph rejection, Applicants submit that the specification clearly teaches the basic and novel characteristics of the invention, and the transitional phrase is therefore partially open and partially closed.

The disclosed invention provides a binding motif to determine which residues of a putative antigenic protein are capable of binding autoimmune associated HLA-DR proteins and activating autoreactive T cells. As stated above, independent claims 3 and 13 are intended to embrace polypeptides capable of binding autoimmune associated HLA proteins, not a full-length autoantigenic protein as described in Amagai. Thus, Applicants submit that Amagai fails to teach or even suggest the invention recited in claims 3-5.

Although Amagai teaches that desmoglein 3 is the full length autoantigen for pemphigus vulgaris, Amagai fails to teach or even suggest what short peptides make up the self epitopes for pemphigus vulgaris. Applicants submit that inclusion of the full-length 103 kD pemphigus vulgaris antigen protein disclosed by Amagai in the preparations of claim 3 would materially affect the basic and novel characteristics of the preparation and, therefore, the full-length pemphigus vulgaris protein is excluded from the scope of independent claim 3. Applicants further submit that one of ordinary skill in the art would readily recognize that a preparation for tolerization consisting essentially of an isolated peptide capable of binding to HLA-DR and activating autoreactive T cells is superior to a preparation containing a full-length protein.

Claims 13-15 were rejected under 35 U.S.C. § 102(b) as being anticipated by Amagai. The Office action states that "in the absence in the specification of a definition of a 'human polypeptide consisting essentially of ...', the claim language is open, and inclusive of the full-length autoantigen."

Applicants submit that Amagai fails to anticipate pending claims 13-15 for the following reasons. Independent claim 13 recites, in part, a vaccination preparation "that in its native preparation includes a polypeptide having an amino acid sequence corresponding to a sequence motif for an HLA-DR protein ... wherein said preparation is free of a polypeptide corresponding to said sequence" amino acid sequence corresponding to a sequence motif for an HLA-DR protein." As stated above, Amagai fails to teach what portions or segments of the desmoglein 3 protein contain the autoantigen for pemphigus vulgaris. Furthermore, Amagai fails to teach a vaccination preparation which includes antigenic polypeptides of a pathogen and excludes polypeptides that activated autoreactive T cells from a subject having an autoimmune disease. Thus, Amagai does not anticipate claims 13-15.

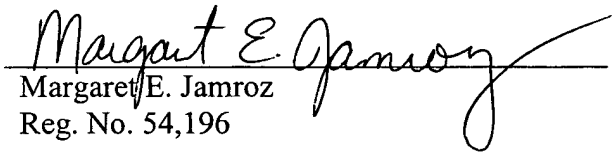
In conclusion, Applicants submit that claims 3-5 and 13-15 are not anticipated by Amagai, and respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: November 4, 2003



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